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Vaccines and the risk of insulin-dependent diabetes (IDDM): potential mechanism of action

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Summary Immunization with a number of different vaccines, including live and killed vaccines, has been linked to the development of insulin-dependent (type 1) diabetes in humans and animals. Multiple different mechanisms have been proposed to explain the association between vaccines and diabetes. The current paper reviews multiple different mechanisms by which vaccines are known to manipulate the immune system and can induce an autoimmune disease such as type 1 diabetes. Genetic variability may determine which of these pathways, or possible other pathways, predominate in an individual following immunization. © 2001 Harcourt Publishers Ltd

INTRODUCTION

Vaccine studies have labelled a vaccine safe if it causes few adverse events in a usually small study group followed for no more than 30 days post-immunization. Data linking vaccines to a rise in a wide variety of immunological diseases such as type I insulin-dependent diabetes mellitus (IDDM) (1–3) and asthma has outlined the pressing need for rigorous long-term vaccine safety studies. It is becoming increasingly clear that the effect of vaccines on the immune system is much more complicated than originally believed, underlining the inadequacy of current safety studies, because vaccines differ from the infections they prevent and have different effects on the immune system. For example, vaccines often contain aluminum adjuvants and are often given intramuscularly, while infections often occur on the surface of a mucous membrane. The vaccine recipient is exposed to a large bolus of immunogens from many different pathogens at once, while natural infections occur with a single pathogen at a time.

IDDM is an autoimmune disease induced by a variety of environmental stimuli (4) and a marker for other immunological diseases. Recently data has been published linking the timing of pediatric immunization to the development of IDDM (1,5,6). According to this data, immunization at birth is associated with a decreased risk of IDDM, while immunization starting after 2 months is associated with an increased risk of IDDM. Mechanisms by which vaccines may impact the development of IDDM are discussed below.

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MOLECULAR MIMICRY

Previous research on vaccine-induced autoimmunity focused on vaccines containing molecules that immunologically mimic autoantigens. These foreign antigens induce antibodies that cross-react to self-antigens. One example is the neural tissue-derived rabies vaccine, which contained neural antigens that induced an autoimmune encephalitis in recipients (7). The whole-cell pertussis vaccine (8) and the BCG vaccine (9) contain heat shock proteins that cross-react to pancreatic islet cell proteins

and may induce IDDM. Molecular mimicry, however, does not explain the variety of autoantibodies that arise after vaccination (10–13). This indicates vaccines may alter autoimmunity by antigen-nonspecific mechanisms, as discussed above.

VACCINE-INDUCED ALPHA INTERFERON RELEASE

It is generally accepted that vaccines are potent immune stimulants. One mechanism by which vaccines can stimulate the immune system is through the release of interferons. Individuals receiving vaccines develop fevers, fatigue, weakness, headache, sweating and myalgia. These symptoms are similar to patients receiving interferons including fever, myalgia and headache. Many vaccines activate macrophages and macrophages release alpha interferon. Alpha interferon is released from macrophages after activation. Alpha interferon has been repeatedly reported to cause IDDM in humans (14–17). One of 40 patients receiving alpha interferon in a Japanese study developed anti-islet cell antibodies (17). An Italian study found 14 of 11241 patients receiving alpha interferon developed diabetes mellitus (18).

VACCINE-INDUCED LYMPHOKINES OTHER THAN ALPHA INTERFERON

Vaccines can cause the release of lymphokines including interferons, interleukins (IL) and tumor necrosis factor (TNF), which can induce IDDM and other autoimmune diseases. Lymphokines may increase the risk of IDDM by directly killing islet cells, speeding a subclinical inflammatory process, altering development of the immune system, and influencing thymus selection of lymphocytes. Proinflammatory cytokines including IL-1, TNF alpha, alpha interferon and type 1 cytokines (interferon gamma, TNF beta, IL-2 and IL-12) have been associated with causing islet cell damage (19). The DTP vaccine has been shown to increase tumor necrosis factor in mice (20,21).

Patients receiving IL-2 and interferons have developed numerous autoimmune diseases, including organ-specific autoimmune diseases, rheumatoid diseases and IDDM (22–26). IL-2 (27,28), IL-1 and TNF are toxic to islet cells in vitro (29,30). TNF is believed to increase inflammation near the islet cells (31), while interferon gamma and IL-6 are believed to be involved in the progression from inflammation to autoimmunity (32). The combination of TNF and gamma interferon increases MHC class II molecules on islet cells which is expected to increase the progression of autoimmunity (33). IL-2 enhances a smoldering autoimmune process but is unable to induce an primary autoimmune response (34).

Administration of lymphokines under certain circumstances has been associated with the prevention of autoimmune disease in rodents and might explain the association between early immunization and a decreased risk of IDDM. Administrations of TNF, IL-1 and IL-2 have all been reported to prevent diabetes in NOD mice under certain circumstances (35–37). Low doses of IL-1 and TNF have been shown to decrease the incidence of diabetes in BB rats (38,39), while both IL-2 and IL-1 have been shown to increase and decrease the incidence of diabetes in BB rats depending on the method of administration (27,38). Early administration of lymphokines may decrease the risk of diabetes by altering the development of the immune system and influencing thymus selection of T lymphocytes (40). Lymphokines may also affect the risk of IDDM by altering viral infections, macrophage function or T helper cell ratios.

T HELPER LYMPHOCYTE RATIOS

Vaccines may influence the risk of IDDM by altering the ratio of the two major T helper lymphocyte subtypes. T helper 1 (Th1) lymphocytes release gamma interferon, IL-2 and TNF. T helper 2 (Th2) cells release IL-4, IL-5, IL-6, IL-10 and IL-13. Th1 activity is associated with destruction of islet cells while Th2 activity is not (41,42). Certain microbial products cause the release of IL-4 and IL-10, which favor the development of Th2 pathways over Th1 pathways (40). High doses of BCG vaccine, for example, may alter the ratio of Th1/Th2 cells in rodents.

MACROPHAGES

Type I diabetics have increased macrophage activity. It is believed that this increased activity precedes the development of IDDM and contributes to the onset of IDDM. Data supporting a causal relationship between macrophage activation and IDDM includes data showing that humans at risk for IDDM because of family history have increased macrophage activity similar to that seen in diabetics (43,44). Animal models indicate that macrophages are involved in the initiation of diabetes (45). Many vaccines activate macrophages and would be expected to increase the risk of IDDM. Vaccines can both directly and indirectly activate macrophages through the release of cytokines. Macrophages are particularly stimulated by vaccine adjuvants including aluminum (46) and complex polysaccharides (47), similar to those found in certain capsular vaccines like pneumococcal and hemophilus vaccines. Insoluble polysaccharides (47) like those found in vaccines are also more potent activators of macrophages than soluble polysaccharides, which may be more common with natural infections.

Macrophages may increase destruction of islet cells by releasing cytotoxic molecules (48,49). Certain macrophages may preferentially increase the replication of Th1 lymphocytes (50) leading to destruction of pancreatic islet cells. Macrophages can injure pancreatic islet cells through the release of free radicals, nitric oxide, and cytokines including IL-1 and TNF (48). Activated macrophages also release alpha interferon. Alpha interferon has been repeatedly reported to cause IDDM in humans (14–17).

Activated macrophages can increase autoimmunity by presenting self-antigens to autoreactive lymphocytes and activating the autoreactive lymphocytes. These autoreactive lymphocytes can kill islets through direct contact with the cells or through the production of soluble autoantibodies which destroy islet cells. The mechanism for inducing autoimmunity appears to involve a lymphokine drive phenomenon, where the vaccine activates the immune systems and an immune response develops to autoantigens that are attached to MHC molecules on the same or adjacent antigen-presenting cells as the vaccine toxoids. This phenomenon appears to occur in the draining lymph nodes (51,52) and is likely to involve both the direct activation of macrophages (46), the release of lymphokines capable of inducing autoimmunity (53) and the up-regulation of lymphokine receptors on cells (54).

ADJUVANT EFFECT

Several investigators working on vaccines to control fertility used the diphtheria and tetanus toxoids, the chief components of the tetanus and diphtheria vaccines, to induce autoimmunity to human chorionic gonadotropin (HCG), in humans. In these experiments the HCG molecule was chemically linked to the diphtheria or tetanus vaccine (55). The ability of vaccines to induce autoimmunity to self-antigens that associate with the vaccine molecules can explain the development of a number of autoimmune diseases following immunization.

Vaccines to prevent pregnancy, which act by inducing an autoimmune response to HCG, have been used in at least four human clinical trials (55). These vaccines consist of human HCG holoprotein or peptides covalently bound to either a diphtheria or tetanus toxoid, the chief component of the diphtheria and tetanus vaccine. The vaccine toxoids were successful in inducing autoimmunity to the human hormone, as demonstrated by the development of anti-HCG autoantibodies in the recipients. Detailed studies in animals show that the association of beta HCG with vaccine toxoids greatly increase the immune response to HCG, as does the use of alum-based adjuvants which are commonly used in vaccines (56). The ability of the vaccines' antigens to induce autoimmunity is not limited to HCG, since a vaccine comprising a diphtheria toxoid covalently linked to a peptide from human gastrin molecule was able to induce antigastrin antibodies in humans (57).

Animal and human experiments show that vaccine antigens, in killed vaccines, do not have to be covalently attached to autoantigens to induce an autoimmune response. Autoimmunity to the testis and thyroid have been induced in both humans and animals when autoantigens have been administered with Freund's complete adjuvant (58,59). Autoimmunity has been induced in animals when Freund's complete adjuvant and the autoantigen are administered in different locations but share the same draining lymph nodes (51,52). Animal studies of this phenomenon show the induction of autoimmunity is not limited to the use of Freund's complete adjuvant. For example, the administration of the swine flu vaccine in combination with a neural extract has lead to the development of autoimmune neuritis, and the administration of the pertussis vaccine with thyroid extract has lead to the development of autoimmune thyroiditis in rodents (60,61). In the latter case, a depot-type adjuvant, Freund's incomplete adjuvant, was necessary for the induction of autoimmunity. Administration of the pertussis vaccine in the absence of autoantigens has been shown to exacerbate smoldering autoimmunity in rodents (62).

The ability of vaccines to induce an autoimmune response to antigens that are in proximity to them explains the induction of autoimmunity in humans following immunization. Vaccine antigens become closely associated with immunoglobulins after entering the body and this explains why rheumatoid factor, an autoantibody against IgG antibodies, frequently develops after immunization (63–66). Antigens from killed vaccines associate with a number of other autoantigens besides IgG, after being administered. For example, antigens from the DTP and other killed vaccines are known to circulate in the bloodstream (67) and associate with the membranes of blood cells causing acute lysis of these cells (68,69). This explains why some who receive vaccines develop an autoimmune response to these cells (70–72). Solid organs may also be affected as well. Vaccination causes myocarditis in up to 3% of healthy patients (73,74). This can be partly explained by circulating antigen precipitating in the heart tissue, however people often develop autoantibodies to myocardial tissue after damage to the heart (75) and this response can be exacerbated by a vaccine draining into a lymph node where the autoimmune process is developing. In either case, the myocarditis induced by vaccination can lead to chronic autoimmune destruction of the myocardial tissue.

Animal studies indicate that, if the recipient has a smoldering autoimmune disease, the vaccines do not have to be closely associated with autoantigens to exacerbate disease (62). This is especially troublesome

since subclinical autoimmunity occurs in at least 2–3% of children based on the presence of autoantibodies (76) and autoimmunity is even more common in adults.

INCREASE IN AUTOANTIBODY TITERS

Autoantibodies to islet cells have been proven to cause IDDM (77–81). Vaccines have been proven to non-specifically increase unrelated autoantibdies, presumably through immune stimulation (10–13). It is thus expected that vaccines would increase the risk of IDDM.

LIVE VACCINES

It has been proposed that both the mumps and rubella (82–84) vaccines may infect the pancreatic islet cells and lead to the development of IDDM. Rubella infections (82,85,86) are known to cause IDDM and many believe that mumps infections also cause diabetes (87). It is proposed that the rubella and mumps vaccine viruses resemble the natural viruses enough to cause IDDM. The best supporting data for a direct infection of islet cells comes from data showing that the rubella virus can infect islet cells grown in culture (86).

Vaccine-induced viral release and IDDM

Immunization with the tetanus (88), hepatitis B, and influenza vaccines have all been shown to cause blood viral titers to increase in patients with HIV (89). The mechanisms include increased viral replication and release (90). The phenomenon does not appear to be specific for HIV and thus persons persistently infected with other viruses are likely to have a similar effect. It is thus probable that, in individuals chronically infected with certain IDDM-causing viruses, vaccines could cause the multiplication and/or release of these viruses into the blood, which could then infect islet cells. The rubella virus is known to cause IDDM (82,85,86) and there is now evidence that other viruses can cause IDDM, in particular Coxsackie B viruses. It is thus likely that in some people infected with viruses, vaccines make the viral infection worse and lead to IDDM.

Data has been published indicating that type I diabetics in a country tend to be born more frequently in certain months (91). This can be explained by viral infections of the newborn or pregnant mother during these months, since certain viral infections tend to be epidemic in certain months. This theory is based on data that congenital rubella infections lead to an increased risk of IDDM (82,85,86).

Dahlquist (92) and others (93) have shown that viruses beside rubella, in particular enteroviruses, are likely to cause IDDM through the same infectious route. Vertically transmitted Coxsackie B virus infections which have been attributed to causing 27% or more cases of insulin-dependent diabetes (92). Dahlquist (94) presented additional data from her studies on maternal infections and the risk of IDDM.

Vaccines may also stimulate the expression of retroviral antigens on the surface of islet cells or macrophages, leading to an immunological attack against the pancreatic islet cells. A retroviral gene in humans, associated with the development of IDDM, codes for a super antigen (95). Super antigens cause polyclonal lymphocyte activation and polyclonal activators have been associated with an increased risk of autoimmunity. Vaccination after 2 months of life may cause the expression of this retroviral antigen, leading to the development of IDDM, while vaccination at birth may cause expression at birth, leading to immunological tolerance and prevention of IDDM.

NATURAL INFECTIONS

Natural infections are known to increase the risk of IDDM (91,96). Therefore it is expected that vaccines would increase the risk as well. Humans suffering from natural immune suppression are at increased risk for developing autoimmune diseases (97,98) and some vaccines (99) have been associated with immune suppression. Vaccination-induced immune suppression could lead to an altered risk of IDDM, possibly by allowing chronic infections with certain diabetes-causing viruses. Vaccines may also lead to an increased risk of IDDM by eliminating natural infections which prevent immune-mediated disorders (100). Living in a more sterile environment may increase the risk of diabetes in humans (101) and rodents (102).

Immunization starting at birth may prevent IDDM by releasing interferon, which can nonspecifically prevent or decrease vertically transmitted virus infections (103). This mechanism may explain why immunization at birth prevents diabetes in NOD mice and BB rats, since both are reported to be infected with retroviruses.

DIFFERENCE BETWEEN NATURAL INFECTIONS AND IMMUNIZATION

Vaccines differ from natural infections in several respects, so it is understandable that they have different effects on the development of IDDM. While naturally acquired foreign antigens such as infections (104) may also lead to induction of autoimmunity, animal and human experiments have shown the use of depot-type adjuvants, as well as repetitive administrations, intensifies the induction of autoantibodies (55,56). Vaccines are often given intramuscularly while infections often occur on the surface of a mucous membrane. The recipient of a vaccine is

exposed to a large bolus of immunogens at once while in natural infections exposure to immunogens occurs more gradually as the pathogen replicates on the surface of a mucous membrane and the immunogens slowly cross the mucous membrane barriers. Children may receive vaccines against five or more diseases at one time, while it is highly unusual for a child to develop more than one of these infections at one time.

All of these differences would be expected to cause differences in the secretion of corticosteroids by the adrenal gland. The adrenal gland is one of the body's key systems to prevent autoimmunity. Adrenalectomy has been shown to exacerbate autoimmunity in both humans (105) and rats (106). Adrenal corticosteroids, by contrast, are used to treat almost all autoimmune diseases. It takes about 3 days for the adrenal glands to increase production of corticosteriolds. This time-frame is adequate for preventing exacerbations of autoimmunity following infections, because it takes several days for the infection to invade the host, multiply to large numbers and stimulate the immune systems. By contrast, the adrenal gland is not well suited for preventing autoimmunity following vaccines, because the immune system is exposed to large amounts of immunogen immediately following immunization and the immune stimulation occurs quickly.

CONCLUSION

There are many mechanisms by which vaccines may affect the onset of IDDM or other immune-induced disorders. The predominant pathways may depend on individual genotype. We believe that lack of full comprehension of the mechanisms of action does not detract from toxicology data linking vaccines to IDDM, nor does a complete knowledge of the mechanism of action need to be known before studying the potential benefits of new immunization schedules.

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